IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/937,899	Confirmation No.: 5535
Applicant	:	Markku KOULU et al.	
Filed	:	28 September 2001	
TC/A.U.	:	1632	
Examiner	:	Robert M. Kelly	
Attorney Docket No.	:	2630-111	
Customer No.	:	6449	

Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL RESPONSE

Dear Sir:

Further to the Request for Reconsideration filed on 30 September 2004 and the Amendment After Final filed on 30 August 2004, Applicants offer the following additional comments for consideration by the Examiner for the above-identified application.

In the Office Action mailed 30 June 2004, the Examiner rejected claims 8 and 14-15 under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants submit that the claimed subject matter as set forth in amended claims 8 and 14 and in new claim 16 is fully enabled by the specification for the reasons set forth in the Amendment After Final filed on 30 August 2004, and incorporated herein in their entirety. In addition, to the reasons set forth in that amendment, Applicants further submit that the claimed subject matter is fully enabled for the following reasons.

Applicants reiterate the main point made in the previously filed Amendment After Final, that although Lebedeva et al. (Levedeva, I. and Stein, C.A. (2001). "Antisense Oligonucleotides: Promise and reality." *Ann Rev Pharmacol Toxicol* **41**:403-419) describes difficulties associated with antisense therapy in the context of specific therapies, such as the passages cited by the Examiner, it also describes techniques that have been used to overcome such difficulties. The fact that Lebedeva et al. describes techniques to overcome the noted difficulties demonstrates that solutions to

difficulties can be achieved without undue experimentation, the only issue to be resolved in determining enablement. It is submitted that Lebedeva et al. clearly shows that any experimentation may be necessary is not undue.

The problems and solutions noted by Lebedeva et al. are recapped as follows.

(a) While Lebedeva et al. disclose problems with phosphodiester oligonucleotides and others, it discloses solutions to these problems. See pages 404-408.

(b) While Lebedeva et al. discusses problems with irrelevant cleavage by RNase H, it discloses a solution to these problems, such as the use of shorter olignoculeotides and other techniques. See page 410.

(c) While Lebedeva et al. discusses the difficulty of delivery of the antisense oligonucleotides, it discusses solutions to overcome this difficulty. See pages 411-412.
Although Lebedeva et al. describes several problems and difficulties, it describes solutions to each of these, and as a result demonstrates the high level of skill in the art for developing antisense oligonucleotides that circumvent the problems that have arisen in antisense therapy.

Furthermore, Applicants note that the Examiner based his conclusions on a single reference (Lebedeva et al.). Specifically, the Examiner concludes that the skilled artisan could not reasonably predict that enough nucleic acid would reach the target site, in large enough amounts, and have enough of an effect, without causing other unexpected effects which would preclude any therapeutic effect from occurring, and that such would occur for a long enough period of time to effect treatment. The Examiner mentions that the referred article discloses several problems associated with any antisense therapy, such as nuclease sensitivity, drug delivery aspects, unwanted and unexpected effects, costs of selection of active sequences is laborious and expensive, and that the field is still immature. Based on above, after full consideration, the Examiner found the claimed subject matter not to be enabled.

With all respect to this scientific opinion based on the Lebedeva et al., Applicants submit that it is still precarious to draw very confident conclusions based on a single scientific article. The

criticism raised by the Examiner is one-sided and solely skeptic. It does not realistically represent the current understanding of the possibilities and weaknesses in the antisense therapy field. There are already a number of examples where antisense oligonucleotides have been applied to the study of mammalian physiology, ocular physiology and ocular disease and there is already one antisense oligonucleotide approved for clinical use in the treatment of cytomegalovirus (CMV) retinitis. This antisense based therapy (Fomivirsen) for human use was accepted already in 1999. Currently there are several antisense based therapies under development. 17 products are in clinical development based on a recent review (Winkler, K.E. (2004). "Killing the Messenger." *Nature Reviews Drug Discovery* **3**:823-824). Therefore the field can not be considered immature and does not solely present an unpredictable nature of the art.

Cost and laboriousness aspect is somewhat irrelevant or at least relative from patenting perspectives. The costs and laboriousness should not affect patentability. In addition the synthesis and selection processes have become more automated, high throughput screening processes, decreasing laboriousness and simultaneously reducing the costs. Furthermore, Applicants submit that selection of the claimed antisense oligonucleotide is not laborious. Applicants have disclosed a specific sequence to which the antisense oligonucleotide should be targeted, i.e., 5'-acaagcgaccgg-3' (SEQ ID NO:9). Applicants have shown that this mutant sequence contains bulbs within the mRNA. See Figure 3 in comparison to Figure 2. A skilled artisan recognizes that bulbs enhance the binding of antisense oligonucleotides to mRNA. Thus, it is submitted that Applicants have fully disclosed the target sequence to which the antisense oligonucleotide is targeted and no laborious selection of antisense oligonucleotides is necessary. Thus, no undue experimentation is required to select the antisense molecule.

Antisense strategy has been used to demonstrate inhibit angiogenesis in the eye (Robinson, G.S. et al. (1996). "Oligodeoxynucleotides inhibit retinal neovascularization in a murine model of proliferative retinopathy." *Proc Natl Acad Sci USA* **93**(10):4851-4856.). Therefore antisense based

therapy can be considered to have therapeutic effect in ocular indications and also in anti-angiogenetic indications, and in anti-angiogenic ocular indications.

Fomivirsen was accepted for human use in an ocular indication. This acceptance also confirms the safety and efficacy of antisense therapy in human ocular indications. In addition, delivery challenges can be overcome by local delivery (e.g. ocular). Also delivery vehicles are useful to deliver antisense molecules in the target site (Jaaskelainen, I. et al. (2004). "Requirements for delivery of active antisense oligonucleotides into cells with lipid carriers." *Methods Enzymol* **387**:210-230.) in order to increase therapeutic antisense amount in the desired site of action.

The field is still maturing and some failures have lead to skepticisms of the utility of the antisense approach, also referred by Lebedeva et al. But there are successful cases, which demonstrate that a therapeutic effect can be achieved by an antisense therapy. The suitability of antisense based therapy on the treatment of ocular angiogenesis has been critically addressed recently by Henry et al. (Henry, S.P. et al. (2004). "Setting sights on the treatment of ocular angiogenesis using antisense oligonucleotides." *Trends Pharmacol Sci* **25**(10):523-527.). Based on the referred publications, the applications for diseases such as ocular angiogenesis are well suited for an antisense based therapy because administration is localized and the compounds have desired pharmacokinetic, pharmacodynamic and safety properties in the eye.

These facts concerning antisense therapy and the eye are further supported by U.S. published patent application number 2004/0006004 A1 (copy supplied with Amendment After Final filed on 30 August 2004) which demonstrates that an antisense oligonucleotide directed to the NPY Y2 receptor mRNA is effective *in vivo* for treating retinopaphy in rats. See especially paragraphs [0005] and [0063] and Figure 3 of the published application. This published application demonstrates that retinopathies can be treated by antisense therapy, i.e., that enough nucleic acid can reach the target site in sufficient amounts for sufficient length of time to yield a therapeutic effect.

In view of the above remarks, as well as the amendments and remarks previously submitted, it is submitted that the claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is requested.

In view of the above remarks and the amendments and remarks previously made, it is submitted that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,
ROTHWELL, FIGG, ERNST & MANBECK, p.c.

By _____

Jeffrey L. Ihnen
Registration No. 28,957
Attorney for Applicants
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
Telephone No.: (202) 783-6040
Facsimile No.: (202) 783-6031

Attachments: Winkler, K.E., *Nature Reviews: Drug Discovery* **3**:823-824 (2004).
Robinson, G.S. et al., *Proc Natl Acad Sci USA* **93**:4851-4856 (1996).
Jaaskelainen, I. et al., *Methods Enzymol* **387**:210-230 (2004).
Henry, S.P. et al., *Trends Pharmacol Sci* **25**(10):523-527 (2004).

111A.suppresp.wpd